Application Status

Please note that the instant application/case has been transferred to examiner Ganapathirama Raghu, Art Unit 1652, whose telephone number is (571)-272-4533 and all further enquiries regarding this application should be directed to said examiner.

In response to the Office Action mailed on 04/16/2008, applicants' filed a response on 07/16/2008. Said response, amended claims 28, 31 and 32. Thus claims 27-33 are pending in this application and are now under consideration.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Withdrawn-Claim Rejections: 35 USC § 112-First Paragraph

Previous rejection of claim 31 under 35 USC § 112-First Paragraph, for enablement and claims 28 and 31-33 for written description is being withdrawn due to claim amendments.

Maintained-Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly

owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over San et al., (Metabolic Engineering, 2002, Vol., 4: 182-192) and in view of Song and Jackowski (J. Bacteriol., 1992, Vol. 174: 6411-6417), Russell and Guest (Biochem. J., 1992, Vol. 287: 611-619), Voet et al., (Biochemistry, second edition, 1995, John Wiley & Sons, Inc., pp. 543-548), Rock et al., (J. Biol. Chem., 2000, Vol. 275: 1377-1387) and Yang et al., (Biotech. Bioeng., 1999, Vol. 65: 291-297). For complete and detailed rejection, please refer to Office Actions dated, 04/16/2008 and 08/07/2007.

Applicants have traversed this rejection with the following arguments:

(A) Applicants have repeated the arguments of 12/07/07 (applicants' response);

(B) Applicants have submitted the following additional arguments in the instant response:

i) Metabolism processes are complex. Multiple processes are often intersected and mingled together to form a network of routes and pathways. Manipulating one particular process often does not produce predictable result if interconnections exist. This phenomenon has been widely documented in scientific articles. For example, applicants have cited a selective section from: page 190 of the article published by Smid et al., (Current Opinion in Biotechnology, 2005, 16: 190-197).

ii) When control of metabolic pathway in intact tissue is studied, every step in the pathway must be considered as a potential site of control. Many of the enzymes in a pathway may be subject to regulation by external factors when studied in isolation but do not regulate flux through the pathway in the cell. Therefore, applicant respectively submits that the current invention is not predictable based on each individual pathway's performance in isolation. For example, applicants have cited a selective section from: In Pantothenate Kinase Control of CoA synthesis in Heart, Robishaw et al., Am. J. Physiol., 1984, 246 (Heart circ. Physiol. 15): H532-H541.

Reply (A): Applicants' arguments have been fully considered but are not deemed persuasive, as argued earlier by the examiner in the Office actions dated 04/16/2008 and 08/07/2007 and continues to hold position that the cited references indeed render the instant invention obvious over cited prior art, as the references provide the Motivation, Suggestion and Expectation of Success:

I. i) San et al., (Metabolic Engineering, 2002, Vol., 4: 182-192) define the pathway wherein the necessary enzymes, substrates that are required for the synthesis of Acetyl-CoA, alterations in Acetyl-CoA levels/fluxes on metabolic flux distribution and the formation of acetic ester in defined bacterial strains expressing different panthothenate kinase activities (especially Fig. 6A and entire document). The seminal findings of San et al., teach metabolic engineering through co-factor manipulation of Acetyl-CoA required as an intermediate for the production of fine chemicals such as Acetyl ester, said strategy involved i.e., a) inactivation of enzymes participating in reactions which compete with Acetyl-CoA

pathways, b) the amplification of enzymes involved in Acetyl-CoA pathways and c) the introduction of heterologous enzymes catalyzing reactions towards increased Acetyl-CoA production; and

ii) Similarly Voet et al., also teach the sequential reactions that are involved in the synthesis of Acetyl-CoA (pages 543-547).

II. Song and Jackowski (J. Bacteriol., 1992, Vol. 174: 6411-6417), Russell and Guest (Biochem. J., 1992, Vol. 287: 611-619), Rock et al., (J. Biol. Chem., 2000, Vol. 275: 1377-1387) and Yang et al., (Biotech. Bioeng., 1999, Vol. 65: 291-297) teach the structural elements such as *panK*, *pdh*, *atf*, *ackA*, *pta* genes that are necessary for the Acetyl-CoA production, promoters such as *lac* and *ptb*, methods of construction of expression vectors comprising said genes under the control said promoters and methods of expression in the desired cellular context and optimal conditions for the growth and increased production of Acetyl-CoA in said engineered microorganisms.

The cited references are in congruence with the obviousness rejection and teach all limitations of the instant claims i. e., meet all the criteria and parameters (Teaching, Suggestion and Motivation) as defined by *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling.

Therefore, the examiner continues to hold the position that the combination of the cited references renders the instant invention obvious for the following reasons. One of ordinary skill in the art would have been motivated to combine the teachings of San et al., (Metabolic Engineering, 2002, Vol., 4: 182-

192) and in view of Song and Jackowski (J. Bacteriol., 1992, Vol. 174: 6411-6417), Russell and Guest (Biochem. J., 1992, Vol. 287: 611-619), Voet et al., (Biochemistry, second edition, 1995, John Wiley & Sons, Inc., pp. 543-548), Rock et al., (J. Biol. Chem., 2000, Vol. 275: 1377-1387) and Yang et al., (Biotech. Bioeng., 1999, Vol. 65: 291-297) to engineer a microorganism in a method for increasing Acetyl-CoA flux by transforming said microorganism *panK*, *pdh*, *atf* involved in the pathway for the production of Acetyl-CoA and disrupting the activity of *ackA* and *pta* that divert the intermediates away from the production Acetyl-CoA and or involved in the catalysis of produced Acetyl-CoA and a skilled artisan would certainly place the said genes involved in the production of Acetyl-CoA under the control of suitable promoters such as *lac* and *ptb* for achieving optimal expression and temporal regulation of the expression of said genes.

The basis for the examniner to continue to hold his position is reasoned below; examiner has provided unequivoical evidence for combining the cited references and that the cited references have been properly applied in this obviousness rejection in accordance with the factual enquires set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling. Furthermore the cited references teach all the limitations of the instant claims.

The cited references render claims 27-33 *prima facie* obvious to one of ordinary skill in the art when one applies the Teaching, Suggestion and Motivation (TSM) test under the rationale for arriving at a conclusion of

obviousness as suggested by the KSR ruling. The rationale applied for this rejection is as follows:

(1) Combining prior art elements according to known method to yield predictable results.

(2) Simple substitution of one known element for another to obtain predictable results.

(3) "Obvious to try"- choosing from a finite number of identified, predictable solution, with a reasonable expectation of success.

The instant invention is a simple combination of elements taught in the prior art, wherein the elements of prior art are combined to yield predictable results and the choice is from a finite number of identified elements with a highly predictable outcome and expectation of success.

Reply (B):

i) Applicant's have cited slected portions of Smid et al., (Current Opinion in Biotechnology, 2005 16: 190-197). Said reference when read in its entirety clearly defines strategies specifically for increasing the production of important co-factors such as Acetyl-CoA, wherein a skilled artisan is taught to consider refining and defining knowledge based strategies for metabolic engineering by understanding the overall metabolism by constructing global metabolic models that capture the existing knowledge of stiochiometric, kinetic and regulatory interactions in the metabolic network (column 2, paragraph 2, page 190 and entire document). The above cited references clearly provide the suggested knowledge such as enzymes, substrates, sequential reactions involved in the

production of Acetyl-CoA and kinetics of the reactions that lead to increased production of Acetyl-CoA as every step in the process is clearly defined and refined. Armed with this knowledge a skilled artisan as matter of routine would employ the instant method of production of Acetyl-CoA and there is high expectation of success and a skilled artisan would also come to the conclusion that the instant method of production of Acetyl-CoA is not of innovation but of ordinary skill and common sense.

ii) Examiner is of the opinion that the reference of Robishaw et al., Am. J. Physiol., 246 (Heart circ. Physiol. 15): H532-H541 is not relevant to the points of contention in the instant application, as said reference is directed to synthesis of Acetyl-CoA in a tissue such as perfused rat heart, wherein none of the genes in the pathway for the production of Acetyl-CoA have been manipulated and the regulation of Acetyl-CoA synthesis in an eukaryotic tissue (organ) is vastly different from the instant method for the production of Acetyl-CoA. The instant method involves a prokaryotic microorganism wherein said microorganism has been engineered for increasing Acetyl-CoA flux by transforming said microorganism with genes such as *panK*, *pdh*, *atf* involved in the pathway for the production of Acetyl-CoA and disrupting the activity of *ackA* and *pta* that divert the intermediates away from the production Acetyl-CoA and or involved in the catalysis of produced Acetyl-CoA.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

Claims 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over San et al., (Metabolic Engineering, 2002, Vol., 4: 182-192) and in view of Song and Jackowski (J. Bacteriol., 1992, Vol. 174: 6411-6417), Russell and Guest (Biochem. J., 1992, Vol. 287: 611-619), Voet et al., (Biochemistry, second edition, 1995, John Wiley & Sons, Inc., pp. 543-548), Rock et al., (J. Biol. Chem., 2000, Vol. 275: 1377-1387) and Yang et al., (Biotech. Bioeng., 1999, Vol. 65: 291-297).

Conclusion

None of the claims are allowable. Claims 27-33 are rejected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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